



<b>Title</b>	<b>Identifying the earliest sign of pathological cognitive decline by using magnetic resonance imaging structural brain connectivity analysis</b>
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**Introduction:** Small-cell lung cancer (SCLC) accounts for 15% of all lung cancer cases. It is notoriously difficult to treat with high relapse rate and the current standard treatment remains chemotherapy. Arginine is an important amino acid in normal human cells that can be replenished through urea cycle, but some tumours are arginine-auxotrophic due to deficient argininosuccinate synthetase (ASS1) and/or ornithine transcarbamylase (OTC). BCT-100 is a pegylated arginase, which converts arginine to ornithine, has demonstrated anticancer activity in human many cancers. We aimed to determine the in-vitro effects of BCT-100 in SCLC.

**Methods:** A panel of seven SCLC cell lines was obtained from ATCC. Cell viability and protein expression were detected by MTT assay and Western blot, respectively. Knockdown of OTC was performed using siRNA. Mitochondrial membrane depolarisation and cell cycle arrest were analysed by flow cytometry.

**Results:** Over-expression of ASS1 in H69 and DMS79 cells, and OTC in H841 cells were associated with resistance to BCT-100. Knocking down of OTC increased sensitivity of BCT-100 in H841 cells partially via apoptosis. H526 cells (BCT-100-sensitive) was selected for mechanistic study. Mitochondrial membrane depolarisation was observed in BCT-100 treatment accompanied by cytochrome c and SMAC release from mitochondria to cytosol. Hydrogen peroxide and superoxide were upregulated in BCT-100 treatment and N-acetylcysteine (reactive oxygen species scavenger) could significantly reversed apoptosis induced by BCT-100. Besides, cyclin A2, cyclin B1 and CDK7 were downregulated by BCT-100 in a time-dependent manner. G1/S arrest was found in BCT-100 treatment by flow cytometry. The expression of p-AKT and p-mTOR was increased after exposure while RAS/RAF/ERK cell signalling pathway was inhibited with BCT-100 treatment.

**Conclusion:** SCLC cell lines with low ASS1 and OTC expression were sensitive to BCT-100 which was partially mediated through oxidative stress, cell cycle arrest, and apoptotic pathway.

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**Introduction:** With the increasing understanding of subjective cognitive decline (SCD) as a possible precursor of mild cognitive impairment (MCI) and Alzheimer's disease (AD), the early identification of those with truly pathological SCD, and distinguish them from normal aging, is of great clinical importance. We investigated this prodromal stage by studying the structural brain connectivity of subjective cognitive impairment (SCI) patients as compared to MCI and healthy subjects.

**Methods:** Patients with SCI (n=29) or MCI (n=33), and healthy controls (n=6) underwent cognitive testing and 3Tesla magnetic resonance imaging (MRI). We performed diffusion tensor imaging-based tractography and brain connectivity analysis on SCI, MCI, and healthy controls. The network topology, network efficiency, and the characteristics of individual brain regions were investigated, then compared between three cohorts. The relations between network metrics and cognitive assessments were also studied.

**Results:** Global network measures did not differ between SCI and healthy controls. However, SCI patients showed significant regional changes in varies brain regions, including orbitofrontal gyrus, rolandic operculum, hippocampus, lingual gyrus, middle occipital gyrus, inferior parietal gyrus, precuneus, superior temporal gyrus, lingual gyrus, inferior parietal gyrus, precuneus, and superior temporal gyrus. More importantly, those regional changes were significantly associated with cognitive assessment scores including Mini-Mental State Examination and Montreal Cognitive Assessment.

**Conclusion:** Our results suggested that cognitive decline-related pathological changes occurred in SCI stage, and MRI structural brain network analysis may be useful for early diagnosis of AD.